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## **Remarks/Arguments**

### **Basis for Amendments to Claims**

Claims 47,48, and 50-73 have been cancelled. Claims 74-92 have been added to set forth what Applicants regard as their invention and to place the claims in condition for allowance or appeal. Inasmuch as the number of claims do not exceed 20 and the number of independent claims do not exceed 3, no additional fees are required for this examination.

Basis for Claim 74 can be found in the specification page 4, lines 17-18 and 32, and page 10, lines 12-13; basis for Claim 75 can be found on page 5, lines 1-4; basis for Claims 76 and 86 can be found on page 4, lines 4-5; basis for Claims 77 and 87 can be found on page 6, lines 6-12; basis for Claims 78 and 88 can be found on page 8, lines 25-26 and page 9, lines 1-2; basis for Claims 79, and 89 can be found on page 6, lines 18-20; basis for Claims 80 and 90 can be found on page 9, lines 3-4; basis for Claims 81 and 91 can be found on page 6, lines 8-9, and 19-20, and page 9, lines 3-4; basis for Claim 82 can be found on page 4, lines 19-20; basis for Claim 83 can be found on page 5, lines 5-6; basis for Claim 84 can be found on page 10, lines 14-30; basis for Claim 85 can be found on page 3, lines 22-24 and page 12, lines 27-30; and basis for Claim 92 can be found on page 4 lines 19-20 and page 5, lines 5-6.

### **Response to Rejection under 35 USC §112**

Claims 56, 57, and 62-73 have been rejected under 35 USC §112 for indefiniteness. More particularly, the Examiner objects that the dependent claims indicate that the excess is based on the weights of the saponin and the formulation containing the saponin while the independent claim indicates that the excess is based on the comparative weights of the saponin and the sterol. This rejection has been rendered moot by the deletion of these claims.

### **Response to Rejection under 35 USC §103**

Claims 47 and 48 were rejected under 35 USC 103(a) as being unpatentable over Vaccine 12(1): 72-80 (Lipford) in view of U.S. Patent 5,583,112 (Kensil). The Examiner asserts that the combined teaching of Lipford and Kensil renders the combination obvious because Kensil discloses that QS-21, which is a purified component of Quil A, is an obvious substitute for Quil A. The Examiner asserts that Kensil provides several reasons to substitute QS-21 for

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Quil A, namely: 1) that QS-21 has adjuvant effects equal to or greater than Quil A; 2) purified saponins showed adjuvant effects at lower dosages than the crude saponin extract; and 3) purified saponins tend to be less toxic (have less hemolytic activity) than Quil A. Applicants disagree with the Examiner's assertions for the following reasons.

The Examiner's logic can be summarized as follows: 1) Kensil discloses that QS-21 is less toxic than, and has adjuvant effects less than or equal to, Quil A; therefore 2) QS-21 is an obvious substitute for Quil A; 3) Lipford teaches to combine cholesterol with Quil A; accordingly, 4) it would be obvious to combine QS-21 with a sterol such as cholesterol.

This reasoning is flawed for a number of reasons: First, QS-21 is one of many components found in Quil A, representing only 3.7% of this crude saponin (see Kensil, Table 1 column 13); therefore, the fact that Lipford discloses the combination of cholesterol and Quil A would not by itself motivate one of ordinary skill in the art to select QS-21 specifically and combine it with an excess of a sterol for any reason. Moreover, it is important to understand what Lipford is trying to achieve: Lipford adds cholesterol to the crude saponin to form an immunostimulating complex (ISCOM), the formation of which is independent of and without regard to the biological properties of Quil A. Rather, the essential characteristic of Quil A that allows it to form the ISCOM is its overall physico-chemical behavior. As Lipford notes, "The protocol for ISCOM formation is essentially the fabrication of *cage-like structures* in the presence of hydrophobic antigen proteins by a dialysis technique." (Page 78, starting at the bottom of column 1, italics added.) Accordingly, one of ordinary skill in the art would not think to replace a complex mixture of over 20 compounds with a particular minor component that represents less than 4% of the mixture to make a similar cage-like structure. On the contrary, the skilled artisan would know that the minor component would bear little physico-chemical resemblance to the mixture from which it was derived. Thus, just as a chef would not think to substitute carrots for an order of chicken soup, the skilled artisan in the field of vaccinations would not be motivated to substitute QS-21 for Quil A.

Accordingly, the Examiner's assertion that QS-21 is less toxic than Quil A is irrelevant because toxicity is not the germane parameter for discovering an alternative material to make the cage-like structures described by Lipford. Furthermore, since Lipford does not disclose any

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comparative toxicity data between Quil A and Quil A in combination with cholesterol, one of ordinary skill in the art would not suspect that the substitution of QS-21 for Quil A in combination with cholesterol would exhibit any benefits leading to the safe use of QS-21.

The Examiner has asserted that the reduced reactogenicity and hydrolysis would be inherent in making the QS-21-containing liposomes suggested by the combination of the cited art. That is beside the point, however. What is relevant is that the Examiner has failed to show how one of ordinary skill in the art would be inclined to combine a sterol with QS-21 based on Lipford's disclosure of Quil A and cholesterol along with Kensil's teaching that QS-21 is less toxic than Quil A. For these reasons, Claim 74 is patentable. Claims 75-84, which depend from and necessarily narrow the scope of Claim 74, are also patentable. Claims 85-93 are also patentable by virtue of their dependency on Claim 74; moreover, these claims are further patentable because neither Kensil or Lipford, alone or in combination, teaches or suggests a method of achieving an immunogenic response using the composition of Claim 74.

For the above-stated reasons, Applicants respectfully request that a Notice of Allowance be granted for Claims 74-93.

Respectfully submitted,



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